The enigma of signet ring cells

"Signet-ring" is a term used to describe the histologic appearance of a cell that presents as a large cytoplasmic vacuole, which compresses the nucleus in the form of a crescent, and the content of the vacuoles is variable (e.g., mucin, lipid, or glycogen).[1] It is seen in association with the basal layer of epithelium, although spinous layer may also be involved.[2] The histogenesis of signet ring cell (SRC) component is unclear. SRCs are an intermediate form of squamous or a glandular or mucin-secreting component.[3] The appearance of signet cells is a result of numerous mucin vacuoles that coalesce and compress the nucleus against the plasma membrane.[4] Ultrastructural examination has unveiled that vacuoles could represent cytoplasmic lumen, cytoplasmic pseudoinclusion, intracellular edema, or hydropic swelling of mitochondria.[1]

SRC change has been found in association with (a) carcinoma cells of the various body sites (gastrointestinal tract, pancreas, breast, lung, urinary bladder, prostate and salivary); (b) noncarcinomatous neoplasms (lymphoma and malignant melanoma); (c) nonneoplastic processes such as stromal nodule of prostate; and (d) precancerous condition such as oral submucous fibrosis (OSMF).[5,6]

SRC could also result from different mechanisms such as mutations in the CDH1 gene, which encodes the important cell–cell adhesion glycoprotein E-cadherin.[7] Mucosal erosion and ischemia as a reactive change of damaged mucosa is another possible mechanism.[8] Although signet change is correlated with aggressive behavior of tumors such as gastric, prostate and ovary carcinoma, literature search has revealed two cases of benign salivary tumors with SRC and few malignant neoplasms such as adenocarcinomas where mucin-containing SRCs unexpectedly behaved as low-grade carcinomas.[1]

Ultrastructural and immunohistochemical studies showed intracytoplasmic lumens lined by a layer of short microvilli and positivity of the vacuole borders for epithelial membrane antigen and associated with the production of a secretory material. However, in these two cases, such production was not observed. This fact could be due to the removal of luminal substance during tissue processing, which leads to the empty appearance of cytoplasmic vacuoles. Immunohistochemical staining for keratin and alpha smooth muscle actin can be positive for SRCs.

Similarly, signet change has been reported in oral precancerous lesions such as OSMF [Figures 1 and 2], yet there is very limited data regarding their origin and mechanism of formation. Early studies on OSMF done in 1963 and 1964 by J. J. Pindborg and Sirsat involved four epidemiologic surveys on oral precancerous lesions which revealed atrophic epithelium exhibiting signet cells in 13% of cases.[6] In January 1970, studies done on 53 biopsies of suspected OSMF cases of 51 Indian villagers

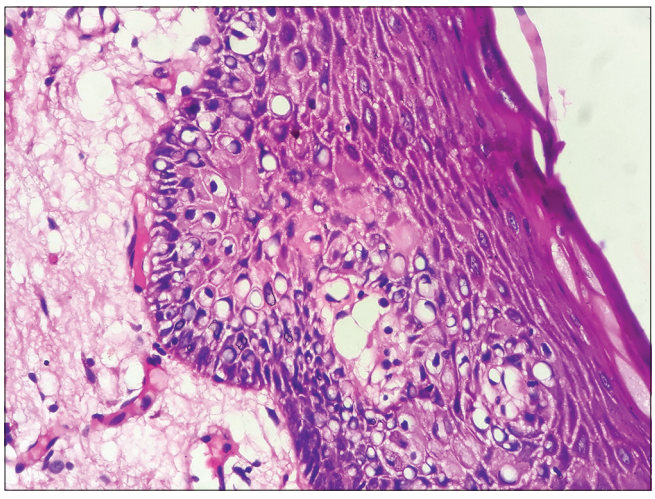

Figure 1: A photomicrograph of oral submucous fibrosis showing signet ring cell change (H&E; ×40)

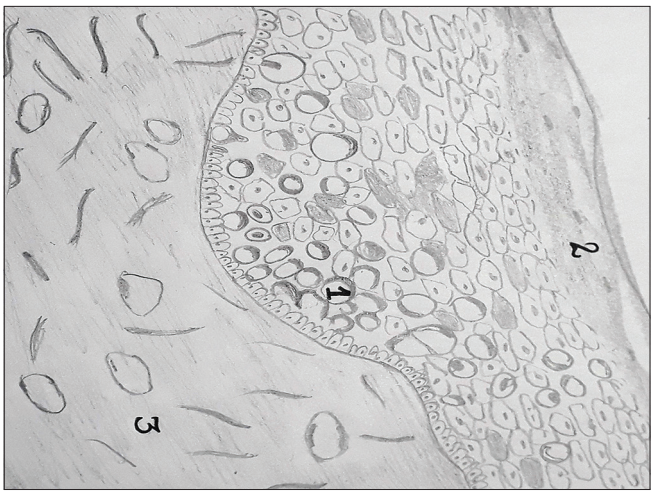

Figure 2: A hand-drawn illustration of signet ring cell change in oral submucous fibrosis ([1] Signet ring cell, [2] epithelium, [3] connective tissue)

by Pindborg, Mehta and Daftary revealed 19.2% biopsies of OSMF, exhibiting a considerable number of signet cells, mostly in basal layers.[9]

In 1976, Pindborg *et al.* reported in detail the epithelial changes in OSMF, by studying 34 biopsy specimens and noticed in 91% of the cases a marked atrophy of the epithelium. Signet cell degeneration in the spinous cell layer and slight liquefaction in the basal cell layer were also observed.[2]

Hence, it was decided to evaluate this signet change in OSMF by staining with PAS, Mucicarmine and Alcian blue, which was negative for mucin, suggesting that it could be lost during processing, giving it the appearance of an empty vacuole. A possible hypothesis for formation could be mucosal erosion and ischemia as a reactive change of damaged mucosa. Although the mystery still shrouds the origin and presence of the signet cells, further evaluation is mandatory to decipher their origin.

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Conflicts of interest

There are no conflicts of interest.

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